US Army Medical Research and Materiel

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Buforin I as a Specific Inhibitor and Therapeutic Agent for Botulinum Toxin B and Tetanus Neurotoxins

Features and advantages:

- **Can prepare using chemical synthesis or recombinant DNA expression systems**
- **Could use selective inhibition to detect BoNT/B and tetanus toxin in assays**
- **Could link Buforin I to the BoNT/B heavy chain with a disulfide bond or a carrier protein**
- **Could administer Buforin I alone or mixed with additional protease inhibitors or adjunct chemicals**

Patent Status

sprinkled over food or wounds to detoxify

Point of Contact

This invention relates to the discovery and preparation of a new class of peptide and peptide-like compounds, “Buforinins”, and specifically to the Buforin I compound. Buforin I has an internal QF cleavage site which enables it to competitively inhibit Botulinum neurotoxin (BoNT) B protease activities at the same site in animal cells. Since the tetanus cleavage and the BoNT/B cleavage sites are the same, Buforin I may also competitively inhibit tetanus protease activity.

The BoNTs are among the most potent toxins to animals and humans, *e.g.*, the lethal dose required to kill 50% of mice exposed to BoNTs (LD_{50}) is about 1 ng/kg. BoNTs comprise a family of seven distinct serotypes, A – G. BoNTs are composed of two subunits, a 100 kdal nerve-cell targeting heavy chain and a 50 kdal endoproteolytically active light chain. The BoNTs are zinc metalloproteases and contain a zinc protein binding motif, HEXXH. Zinc metalloprotease inhibitors exist but are not effective against BoNTs; they merely delay the protease activity *in vivo*. Inhibitors of the various serotypes, including BoNT/B, are therefore needed. BoNT/B specifically cleaves synaptobrevin (VAMP2) at the QF cleavage or bond site between glutamine 76 and phenylalanine 77; however, more than the recognition of the QF cleavage site by the toxin is required for substrate [illegible]e or inhibition.

Subjects could potentially be treated with an intravenous injection or a patch prior to situations where contact with BoNT/B or tetanus toxins is likely. Buforin I could [illegible]ly be incorporated into a disposable, moist-filter, breathing mask for inactivating BoNT/B in an aerosol form. Buforin I was shown in a rat model to be a long-lived peptide, *in vivo*.

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KEYWORDS: buforin I; buforinin; botulinum; tetanus; inhibitor; peptide; therapy

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